Eighth edition of the American Joint Committee on Cancer staging system: are we getting closer to the ideal classification for gastric cancer?

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For patients diagnosed with cancer, the outcomes are mainly determined by the stage of the disease; while it establishes the risk of progression and the median survival, it also serves as a guide when planning the treatment. Tumor extension and metastases to lymph nodes (LNs) have been proven as the most important prognostic factors; in this regard, the tumor-node-metastasis (TNM) classification is currently recognized as the standard tool for staging malignant solid tumors (1,2). Nevertheless, it is not a perfect system as it has limitations; specifically, in gastric cancer, the 7th edition was criticized for failing to incorporate the two N3 subclassifications into the final stratification despite reports of significant differences (1,3,4). The 8th edition published in 2017 included this key change to the pathologic grouping, dividing the N3 category into N3a (7–15 positive LNs) and N3b (≥16 positive LNs). As a result, stage shifts occurred: on one side, some tumors were upstaged (T1N3bM0 from IIB to IIIB, T2N3bM0 from IIIA to IIIB and T3N3bM0 from IIIB to IIIC); on the other hand, others were downstaged (T4aN2M0 from IIIB to IIIA and T4aN3aM0 and T4bN2M0 from IIIC to IIIB) (5). At first sight, this enabled a widening of the distance between the survival curves and therefore entailed an apparently better classification (2,6); however, the cohort of patients used in creating the new edition might not represent all the populations around the world, since 84.8% of the cases came from Japan and Korea and just 8.8% were from western countries (6).

Multiple studies serving as external validations have been done, the majority of them in Asia (particularly China) but only a few in Europe and the United States. As aforementioned, the modification impacted predominantly patients in stage III and thus they are the focus of the revisions. In general, the most frequent effect was the downstaging of groups (range: 7.9%–37.1%), what could raise concern about an underestimation of their prognosis (1,2,4-8); yet, for subjects who migrated stage, the survival curves had no significant difference compared to those of the classification in which they remained (1,4). Furthermore, N3a and N3b do represent distinctive severities of the disease; with the latter having worse outcomes (2,3,5,7). Data provided by Huang *et al.* showed that the 8th edition grades more orderly locally advanced gastric cancers; uniformly poorer survival rates were observed for all stages III: the median survival was 49, 27 and 15 months for subgroups A, B and C, respectively (per the 7th edition it was 62, 30 and 18 months) (9). Still the results are mixed; even though it has been demonstrated to offer a more accurate stratification (it has better homogeneity, discriminatory ability and monotonicity of gradients; besides, series have concluded its validity for western nations) (4,6,10), Lu *et al.* found that its superiority was only evident when ≥30 LNs are examined (they even propose a new model that depends on the number of LNs harvested) (6,7).

Unfortunately, an adequate lymphadenectomy is not

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always performed; in fact, the TNM system does not define a minimum number of LNs that should be retrieved during the surgery, but solely recommends that at least 15 LN are studied to distinguish the N3 categories. This flaw can lead to wrongly staging 10–15% of cases (11-13). Another tool to overcome the issue must be adopted; the lymph node ratio (LNR), defined as the positive LNs divided by the total LNs examined, has been suggested as a promising alternative. In previous studies, it was attested as an independent prognostic factor that correlated with poorer survival as the score increased, reflecting the tumor's worse biology (11,14). Wu *et al.* concluded that its maximum usefulness was observed for stage III patients; in whom a further separation of survival rates was evident, not so for the rest of the groups (11). Meanwhile, Zhao *et al.* established that this improvement was significant only when the number of LNs was not the optimal (13). The authors of the current paper analyzed its performance in the N3b set and effectively demonstrated it was the most powerful independent indicator of disease behavior (9). All the same, it has limitations as the ideal cutoff values haven't been well determined: on this occasion, the investigators of the article used 0.35 and 0.79; some series have employed 0.20 and 0.50 and others 0.15 and 0.40 (9,11,13). Its addition to the TNM classification may yield enhancements in the accuracy of the staging process (the novel scheme showed a larger concordance index and a smaller Akaike information criterion values) (13-15). Even so, it is important to always remember that no instrument can replace a satisfactory surgical dissection.

In summary, the 8th edition has been validated for its implementation in both eastern and western populations; moreover, research has confirmed it is superior to the previous versions by providing a better stratification of patients with a more precise prognosis (this benefit is mainly noticed in locally advanced cancer as Huang *et al.* stipulated). Now, since the N stage varies according to the amount of LNs obtained by the surgeon and the minimum number required has not been formally standardized, different models should be applied. In this manner, the LNR improves the effectiveness of the TNM system; although the authors evaluated its utility for the N3b category, others have verified its value when <15 LNs are examined. Noteworthy, the available literature continues to have limitations as all the studies are retrospective and consequently are subject to bias; also, some of the subgroups had very few patients and no supplementary tests could be made.

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